Chapter 9

LONG-TERM EVALUATION OF RENAL TOXICITY AFTER PEPTIDE RECEPTOR RADIONUCLIDE THERAPY WITH ^{90}Y-DOTATOC AND ^{177}Lu-DOTATATE: THE ROLE OF ASSOCIATED RISK FACTORS

[1]Lisa Bodei, [2]Marta Cremonesi, [2]Mahila Ferrari, [1]Monica Pacifici, [1]Chiara M. Grana, [1]Mirco Bartolomei, [1]Silvia M. Baio, [1,3]Maddalena Sansovini and [1]Giovanni Paganelli

[1]Nuclear Medicine and [2]Health Physics Divisions, European Institute of Oncology, Milano, Italy; [3]Department of Nuclear Medicine, University of Bologna, Italy.

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Abstract

Peptide receptor radionuclide therapy (PRRT) of neuroendocrine tumours with ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE is promising. The kidney is the critical organ and, despite renal protection, function loss may become evident years later. The aim of this study was to analyse renal parameters in patients who had undergone dosimetry before PRRT. Among those in protocols at our Institution, 28 patients were considered: 23 received ^{90}Y-DOTATOC (3.8-29.2 GBq, median 12.2), and 5 received ^{177}Lu-DOTATATE (20.7-29.2 GBq, median 23.2). Patients were followed up after therapy for creatinine and creatinine clearance loss (CCL) for 3-97 months (median 30). Renal doses and bio-effective doses (BED) were calculated (MIRD, LQ model). After ^{90}Y-DOTATOC toxicity on creatinine according to NCI criteria occurred in 9 cases (7 grade 1, 1 grade 2, 1 grade 3), CCL at 1 year >5% in 12 cases, >10% in 8. A 28 Gy BED threshold was observed in patients with risk factors (mainly hypertension and diabetes), while it was 40 Gy in patients without risk factors. Probably due to the low number of patients, despite the absence of severe toxicity after hyperfractionated PRRT, clear correlations between fractionation and toxicity could not be found. After ^{177}Lu-DOTATATE no toxicity occurred in 1-2 years follow-up, CCL at 1 year >5% occurred in 3 patients, >10% in 2. Our results indicate the importance of clinical screening for risk factors: in this case a BED<28 Gy is recommended. Fractionation of therapy is important in order to decrease toxicity, and further studies are needed to evaluate its clinical impact.

Introduction

Peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogues, such as [^{90}Y-DOTA^{0},Tyr^{3}]-octreotide (^{90}Y-DOTATOC) and, more recently with [^{177}Lu-DOTA^{0},Tyr^{3}]-octreotate (^{177}Lu-DOTATATE), is a promising new tool in the management of patients with inoperable or metastasized neuroendocrine tumours. [1-4].

These compounds are able to irradiate tumours and their metastases via the internalization through a specific receptor subtype, generally over-expressed on the cell membrane. PRRT can deliver radiation doses to tumours, which are adequate to achieve significant volume reduction.

Initial studies were performed with the radiopeptide used in diagnostics, [^{111}In-DTPA^{0}]-octreotide, administered in high activities. Results were encouraging, with frequent symptomatic and biochemical responses, although objective responses were rare (5% partial response) [5]. The radiopeptide that has been most extensively studied is ^{90}Y-DOTATOC. Clinical trials performed in several countries, despite different phase I-II protocols, thus not specifically addressing efficacy, showed complete and partial remissions in 10 to 30% of patients.
In the clinical phase II trial with ^{177}Lu-DOTATATE, which has a higher affinity for the subtype 2 somatostatin receptor, 47% overall response rate was recorded, with a median time to progression of >36 months [6]. Significant biochemical and symptomatic responses in functioning tumours were encountered for both radiopeptides.
Toxicity, requiring renal-protective agents, is generally mild and may involve kidneys and bone marrow. These data indicate that PRRT offers a convincing alternative in the treatment scenario of neuroendocrine tumours.
Due to their marked radiosensitivity to the doses usually achieved during PRRT, the kidneys undoubtedly represent the critical organs, particularly after ^{90}Y-DOTATOC. Renal irradiation arises from the proximal tubular reabsorption of the radiopeptide and the resulting retention in the interstitium. The co-administration of positively charged amino acids, such as L-lysine and/or L-arginine, competitively inhibiting the proximal tubular re-absorption of the radiopeptide, results in a reduction in the renal dose ranging from 9 to 53% [7,8]. Despite kidney protection, renal function loss may become clinically evident years after receptor radionuclide therapy, especially after ^{90}Y-DOTATOC.
The aim of this study was to investigate the long-term behaviour of main parameters of renal function in a sub-group of patients who underwent dosimetry, among those treated in our Institution with ^{90}Y-DOTATOC or ^{177}Lu-DOTATATE in the past decade.

Materials and methods

Patients

From April 1997 to May 2006, among the 211 patients treated with ^{90}Y-DOTATOC and the 25 patients treated with ^{177}Lu-DOTATATE according to our protocols [3], 28 patients (13 f, 15 m, 16-73 years, median 49), affected by somatostatin receptor-positive tumours, mainly neuroendocrine, were selected for dosimetric studies before PRRT and were followed up. Protocols applied in our institution were:
Protocol 1. The phase I protocol of PRRT with ^{90}Y-DOTATOC without amino acid protection, in which patients were divided in groups treated with three consecutive, equal-activity cycles, with activities escalating between groups by 0.37 GBq, from 1.11 to 2.59 GBq per cycle [9].
Protocol 2. The phase I protocol of PRRT with ^{90}Y-DOTATOC with amino acid protection, in which patients were divided in groups treated with two consecutive, equal-activity cycles, with activities escalating between groups by 0.37 GBq, from 2.96 to 5.55 GBq per cycle [10].
Protocol 3. The ongoing, two-step, phase I-II protocol of PRRT with ^{177}Lu-DOTATATE. In the first step, whom these data belong to, patients were divided in

groups treated with consecutive, equal-activity cycles, with groups ranging from 3.7 to 5.18 GBq per cycle, up to a cumulative activity ranging from 22.2 to 29.6 GBq, depending on dosimetry. This study is still ongoing [11].
Patients treated in the first two protocols, which were pure phase I studies, therefore aimed at defining toxicity, performed the first three or two cycles according to the relative protocol, and then completed PRRT up to the cumulative activity needed to deliver a sufficient absorbed dose to irradiate the tumour.
Twenty-three patients received ^{90}Y-DOTATOC, with a cumulative activity of 3.8-29.2 GBq, (median 12.2), while 5 patients received ^{177}Lu-DOTATATE, with a cumulative activity of 20.7-29.2 GBq (median 23.2). Patients' characteristics are summarized in Table 1.
Risk factors described in Table 1 relate to all the conditions known to affect renal function, such as long-standing and partially controlled hypertension and diabetes, age, and renal morphological abnormalities [12-14]. As regard hypertension, the involved patients (#1, 3, 24, and 27) were affected by the essential form (defined by blood pressure values above 140 over 90 mmHg, systolic/diastolic). These patients had benign and long-lasting forms of hypertension, which were under pharmacological control. One patient (# 8) had a particularly severe form of diabetes mellitus, secondary to the pancreatic substitution by the tumour, and was partially controlled by insulin therapy due to a scarce compliance to substitutive therapy and to diet. Renal function deteriorates with age, and age is *per se* an unfavourable factor for patients performing a therapy potentially affecting kidney function. Nevertheless, the effect of age was not analysed in our series. Renal morphological abnormalities relate to all the conditions affecting renal functioning parenchyma, such as large cysts. Other conditions considered as risk factors were trans-arterial chemo-embolisation (TACE), due to renal cortical retention of contrast medium [15] and previous chemotherapy with nephrotoxic agents, such as platinum derivatives [16].

Dosimetry
To allow individual dosimetric analysis, ^{111}In-DOTATOC (185 MBq) was used as surrogate in patients subsequently enrolled to ^{90}Y-DOTATOC therapy, while patients recruited to ^{177}Lu-DOTATATE were studied directly during the first course of therapy. Blood samples, urine collection and serial whole body (WB) images (^{111}In / ^{177}Lu energy windows, 20%) were obtained up to 48 – 72 h p.i. WB transmission (^{57}Co-flood source) and low dose CT-scans were acquired for individual attenuation and actual organ mass corrections [17-19]. Images were analysed by the conjugate view technique with attenuation, scatter, background, and physical decay corrections. Counts in WB images were normalized at the first image (100% of the injected activity) [20]. The effective half-life of the radiopharmaceutical for the kidneys was evaluated for each patient, assuming a mono-exponential trend of the time-activity curve. The number of disintegrations in all source organs was calculated by a compartmental model (SAAMII) for both ^{177}Lu- and ^{90}Y- derivatives to assess the absorbed doses (OLINDA/EXM), with the inclusion of the patient specific masses [21-23].
The linear quadratic model revised for radionuclide therapy [24] was considered to evaluate, for every patient, the biological effective dose (BED) to the kidneys,

depending on the individual renal absorbed dose and number of cycles of PRRT. The following equation was applied:

$$BED = \Sigma_i D_i + \beta/\alpha \cdot T_{1/2\ rep} / (T_{1/2\ rep} + T_{1/2\ eff}) \cdot \Sigma_i D_i^2 \ ,$$

where Di is the kidney dose delivered per cycle i; α/β is the parameter which relates the intrinsic radiosensitivity (α) and the potential sparing capacity (β) for the kidney tissue and which was set as α/β = 2.6 Gy; $T_{1/2\ rep}$ is the repair half-time of sub-lethal damage ($T_{1/2\ rep}$ = 2.8 h); $T_{1/2eff}$ is the patient specific effective half-life of the radiopharmaceutical in the kidneys [18,25,26].

Renal parameters

Patients had basal creatinine values ranging from 0.44 to 1.05 mg/dl in females and from 0.64 to 1.06 mg/dl in males. Basal creatinine clearance values, calculated according to the Cockroft-Gault formula, ranged from 144 to 42 ml/min in females and from 155 to 70 ml/min in males.

Twelve patients treated with ^{90}Y-DOTATOC had risk factors for renal toxicity, including hypertension, diabetes, previous chemotherapy, liver chemoembolization, and renal or peri-renal lesions (therefore contributing to irradiate the kidneys). None of the patients treated with ^{177}Lu-DOTATATE had any known risk factor.

Patients were followed up for renal toxicity by measuring creatinine and creatinine clearance according to the Cockroft-Gault formula. Creatinine toxicity was measured according to NCI criteria: grade1 = ULN-1.5 · ULN; grade 2 = 1.5-3 · ULN; grade 3 = 3-6 · ULN; grade 4 = >6 · ULN). Creatinine clearance loss was calculated as the % loss in creatinine clearance, in a 3-97 months follow up (median 30) after therapy. Creatinine clearance loss was calculated at every creatinine sample after the basal one. The maximum loss in creatinine clearance was obtained from the whole series of data. Creatinine was measured monthly during therapy cycles and every 3 months thereafter. The follow-up period was considered to be ended either when patients started other potentially nephrotoxic therapies, were lost to follow-up or died.

Statistical methods

The possible relationships between variables, namely the presence of risk factors, or the administered cumulative activity, the kidney absorbed dose, the kidney BED, the number of cycles and the occurrence of renal toxicity or creatinine clearance loss, were evaluated with the Chi Square Test (Test for Independent Samples) and *t* test, by means of the statistical software SPSS v. 15.0. To build contingency table for chi-square test, the variables have to be dichotomous. The medians were the cut-offs used to analyse, by means of chi-square test, the relationship between the variables (kidney BED, kidney dose, cumulative activity and number of cycles) and toxicity.

t test for Independent Samples was used to evaluate a possible significance in the relationship between creatinine clearance loss and BED.

Results

Kidney parameters, absorbed doses and BED results for each patient are summarized in table 2.

In a follow-up period of up to 8 years, patients treated with ^{90}Y-DOTATOC showed creatinine toxicity in 9 cases (7 of grade 1, 1 of grade 2, 1 of grade 3; figure 1), starting 1-5 years after radionuclide therapy. Eight of the 9 patients showing toxicity had pre-existent risk factors. The remaining patient had no risk factors and was the only one showing a recovery from creatinine toxicity 3 years after the onset (Table 3). Creatinine clearance losses >5% at 1 year occurred in 12 cases, >10% at 1 year occurred in 8 cases. Higher (>30%) losses of creatinine clearance occurred in patients showing toxicity. The chi square test (test for independent samples) demonstrated that toxicity was statistically correlated to kidney BED: with one degree of freedom, the P value was 0.036 (Fisher's exact test), and therefore <0.05. Chi square test did not demonstrate any significant relationship between toxicity and the absorbed dose (P=0.68, Fisher's exact test) or the cumulative activity (P=0.67, Fisher's exact test).

Figure 2A shows the course of creatinine clearance in the 23 patients treated with ^{90}Y-DOTATOC over an 8-year period. Due to the lack of such a long observation in all patients, the analysis was focused on a 4-year period (figure 2B), in order to test the actual effect of risk factors in the onset of renal toxicity after PRRT: two separate analyses were performed for patients with (n=12, red line) and without risk factors (n=11, blue line). Patients with risk factors had wider and persistent reductions of creatinine clearance (up to 73%, median 26) than did patients without risk factors (up to 13%, median 9), who instead showed a tendency towards recovery after 2 years.

None of the patients treated with ^{177}Lu-DOTATATE had any toxicity at the time, the follow-up being shorter than in the previous group, namely 1-2 years. Nevertheless, creatinine clearance losses >5% at 1 year occurred in 3 patients, >10% at 1 year in 2 patients. Figure 3 shows the course of creatinine clearance in these patients.

Due to the relatively short follow-up and number of patients treated with ^{177}Lu-DOTATATE, we focused further analyses on the patients treated with ^{90}Y-DOTATOC.

The analysis of creatinine clearance loss in relation to the biological effective dose (BED) shows that, regardless of the dose received by the kidneys, the loss is more evident (P=0.005 and, therefore, <0.05; *t* test for independent samples) in patients with risk factors (hypertension, diabetes, age, and renal morphological abnormalities; Figure 4A).

Likewise, the analysis of creatinine toxicity in relation to the BED showed that toxicity occurred almost exclusively ($p<0.05$; chi square test) in patients with risk factors. In these patients, the observed BED threshold for renal toxicity, namely the lowest value of BED above which we observed toxicity in our series, was 28 Gy, while in patients without risk factors the observed BED threshold for toxicity was 40 Gy (Figure 4B).

Considering creatinine toxicity in relation to the BED and the number of cycles into which the therapy is divided, despite the absence of severe toxicity in patients who received a hyper-fractionated therapy, a clear statistic correlation could not be found (chi square test for independent samples) between toxicity and the number

of cycles, probably due to the relatively low number of observations (Figure 5). Toxicity also occurred even in patients treated with high number of cycles, but these patients had pre-existent risk factors. With a higher spread of the observations, the same holds true for creatinine clearance loss (chi square test for independent samples). In this case as well, despite the presence of more severe losses in patients receiving a hypo-fractionated treatment, a clear statistical correlation could not be found.

Discussion

Renal irradiation arises from the proximal tubular reabsorption of the radiopeptide and the resulting retention in the interstitium. Due to their marked radiosensitivity to the range of doses resulting from PRRT, the kidneys represent the critical organs. This effect is particularly marked after [^{90}Y-DOTA^{0},Tyr^{3}]-octreotide, due to the higher energy and wider range of beta particle penetration of ^{90}Y in tissue (E_{max}: 2.27 MeV, R_{max}: 11 mm). ^{177}Lu, whose beta particles possess lower energy and shorter penetration power in tissue (E_{max}: 0.49 MeV, R_{max}: 2 mm), results in lower kidney doses and therefore a reduced occurrence and severity of renal toxicity [6].

Sporadic cases of delayed renal failure, in some cases end-stage requiring dialysis, have indeed been observed, especially in patients who have received activities >7.4 GBq/m^2 in very few cycles with no kidney protection [27,28]. Given the high retention of radiopeptides in the kidneys, appropriate methods of reducing renal uptake have been applied, in order to avoid acute or delayed renal toxicity. Positively charged amino acids, such as L-lysine and/or L-arginine, competitively inhibit the proximal tubular re-absorption of the radiopeptide, and result in a reduction of the renal dose ranging from 9 to 53% [7,8]. Doses are further reduced by up to 39% by prolonging infusion over 10 hours and by up to 65% by prolonging it over two days after radiopeptide administration, thus more extensively covering the elimination phase through the kidneys [3,10].

Despite kidney protection, renal function loss may become clinically evident 1-5 years after receptor radionuclide therapy. A median decline in creatinine clearance of 7.3% per year has been calculated in patients treated with ^{90}Y-DOTATOC and of 3.8% per year in patients treated with ^{177}Lu-DOTATATE. Cumulative and per-cycle renal absorbed dose, age, hypertension, and diabetes are considered as factors accelerating the decline of renal function after PRRT [29].

Renal failure in its various degrees, up to the end- stage requiring dialysis (which is fortunately rare owing to renal protection), is a remarkably untoward event. It is important to avoid such toxicity particularly in patients with neuroendocrine tumours, whose life expectancy is relatively long and allows various treatments to be attempted besides PRRT.

Kidney radiation toxicity is typically evident several months after irradiation, due to the slow repair characteristics of renal cell. According to studies on renal toxicity derived from external radiotherapy (those referred to by the nuclear medicine community, up to a few years ago), the accepted renal tolerated dose is in the range of 23-25 Gy. As stated by the National Council on Radiation Protection and Measurements – NCRPM – in fact, a dose of 23 Gy to the kidneys causes detrimental deterministic effects in 5% of patients within 5 years [30,31].

Nevertheless, clinical experience and dosimetric studies clearly indicate that this renal dose threshold does not accurately correlate with the renal toxicity observed in patients undergoing PRRT [26].
In PRRT with ^{90}Y-peptides, dosimetry cannot be reconstructed from the bremsstrahlung images, due to the lack of the gamma emission needed for the quantitative analysis. Therefore, two alternative approaches have been developed as surrogate for the original radiopeptide, namely the therapy simulation with the ^{111}In-labelled peptide and the one with the ^{86}Y-labelled peptide. In this study, the dosimetric simulation for ^{90}Y-DOTATOC was performed with ^{111}In-DOTATOC. ^{90}Y- and ^{111}In-DOTATOC are not chemically identical, the latter has been used for dosimetric simulation, basing on the hypothesis that the similar physical and biological half-lives yield a comparable *in vivo* pharmacokinetics and biodistribution, especially concerning the renal uptake, which depends on aspecific phenomena. Although literature lacks an actual comparison study between ^{111}In and ^{86}Y simulation approaches, the pharmacokinetic parameters were similar, as well as the kidney dose [32,33].
PRRT is a form of continuous radiation delivery with a decreasing dose-rate with time. The irradiation produces both lethal and sub-lethal damage, that can be repaired during the irradiation itself, but the differential between creating new damage and the repairing depends on the specific dose-rate at any particular time and on the repair capability ($T_{½rep}$) of the tissue. Low dose-rates, as in PRRT, will spare normal tissues more than the tumour, and this may allow benefits as in fractionation in external radiotherapy [34].
The linear quadratic model interprets mathematically this differential sparing and the biological effective dose (BED) concept is used to quantify the biological effects induced by different patterns of radiation delivery. This model has been recently revised for radionuclide therapy [19] and has been applied in particular to PRRT with the intent of increasing the dose-response correlation. Focusing on the kidney concern, the BED has proven to be a reliable predictor of renal toxicity, helpful in the implementation of individual treatment planning [26]. However, BED is a relatively young concept applied to nuclear medicine and has still to be fully validated with a wider series of data.
The main radiobiological parameter required in such assessment is the tissue α/β ratio, which gives an indication of the sensitivity of a tumour or normal tissue cell to the effect of dose-rate (and/or fractionation), and is generally higher for tumours (5-25 Gy) than for late-responding normal tissues (2-5 Gy). Additional parameters introduced in the refined expression for the BED ($T_{1/2\ rep}$; $T_{1/2\ eff}$) allow to take into consideration the effect of the repair potential, of the dose rate and of the delivery of the dose – which is protracted, and possibly divided in cycles.
Tissues with low α/β values, such as the kidneys, are more influenced by small changes in the dose-rate or dose per fraction than tissues with high α/β values, such as tumours. Therefore, from a radiobiological point of view, it seems particularly important to fractionate elevated amounts of radioactivity in more cycles to allow the sub-lethal radiation damage repair in normal tissue.
Our data on toxicity and loss of creatinine clearance are consistent with other experiences reported in literature regarding the constant and progressive loss of renal function with either radiopeptides, more marked after ^{90}Y-DOTATOC [29]. Remarkably, in our series the large majority of the cases of toxicity occurred in

patients with pre-existent risk factors, with a tendency to persist with time, whilst the only patient without risk factors experiencing toxicity, recovered over a 3-year time period.
The analysis of creatinine clearance loss in relation to the BED shows that, even with equal BED delivered to the kidneys, the loss is more evident in patients with risk factors (hypertension, diabetes, age, and renal morphological abnormalities).
Likewise, the analysis of creatinine showed that toxicity occurred almost exclusively in patients with risk factors. In these patients, the BED threshold for renal toxicity was 28 Gy, while in patients without risk factors the BED threshold for toxicity was 40 Gy. These data not only substantiate reports in literature regarding a renal BED threshold of 40 Gy in patients without risk factors [26], but also contribute to quantifying a different threshold in patients with risk factors, and ultimately enrich the still poor statistics on renal effects of PRRT. Moreover, the impact on clinical management is considerable, since this different BED threshold can lead the clinician to a different therapy cycling or even to shift patients with risk factors to ^{177}Lu-DOTATATE.
The exact kidney dose threshold has been extensively questioned in the past, and discussion arouse on whether the cumulative activity should be either fractionated in many low activity cycles or in fewer high activity cycles [3,4]. The present analysis being a retrospective evaluation of patients treated according to different protocols, the therapy schemes are not homogeneous as to the administered activity and the number of cycles. The first two protocols, in fact, were pure phase I studies, therefore aimed at defining toxicity, and patient included completed PRRT after the protocol up to the cumulative activity needed to deliver a sufficient absorbed dose to irradiate the tumour. This is the explanation of such dispersed results. However, the data obtained from the follow up of these patients as to kidney function seemed important to expand the still small knowledge in this field. In any case, the BED concept takes into account differences in administered activity per cycle. Moreover, the sub-division of the cumulative activity, and therefore the dose, in different number of cycles was regarded as a possibility of evaluating the effect of the different variables, including fractionation. However, the predominance of patients with risk factors in our series, represented a bias that probably masked any possible advantage of fractionation, together with the low number of observations and the different administration schedules. Although there seems to be a tendency toward a higher occurrence of creatinine clearance loss and toxicity in hypo-fractionated treatments, we could not find any statistical correlation between the fractionation scheme and the occurrence of toxicity or creatinine clearance loss. From a radiobiological point of view, fractionation is certainly a crucial factor but, in view of these results, it appears to be less powerful than the presence of risk factors. Further studies are needed to evaluate this issue, which seems important and theoretically supported by radiobiological considerations.
Our observation points out the importance of the clinical screening of the patients undergoing PRRT, especially with ^{90}Y-DOTATOC, as regards pre-existing conditions that may affect renal function in the long term. The presence of risk factors, particularly hypertension and diabetes, rather common in the elderly population such as those with neuroendocrine tumours, should suggest accordingly modifying the treatment plan towards caution in choosing cumulative

and per-cycle activity, and therefore the renal dose and, especially, the renal BED, or even switching to ^{177}Lu-DOTATATE. In case of risk factors, patients should undergo dosimetry and should not receive a BED higher than 28 Gy, possibly fractionated in a high number of cycles.

Conclusions

Our observation highlights the importance of the clinical screening of patients undergoing PRRT, as regards pre-existing risk factors, such as hypertension and diabetes. Patients with risk factors should undergo a thorough dosimetric study and should not receive a BED higher than 28 Gy. Fractionating the cumulative activity in a large number of cycles is another crucial point in PRRT to decrease the risk of delayed renal failure. As a future endpoint, the possible benefit of fractionation should be studied in appropriate clinical trials.

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Table 1. Characteristics of the 28 patients, as regards pre-existing risk factors, therapy and protocol number.

Patient #	Tumour	Risk factors	Therapy	Cumulative activity (GBq)	Protocol
1	Pancreas NET	TACE, HT	Y-TOC	11.5	2
2	Medullary thyroid carcinoma		Y-TOC	19.2	2
3	Bronchial NET	TACE, HT, renal cysts	Y-TOC	12.2	2
4	Bronchial NET		Lu-TATE	29.2	3
5	Pancreas NET		Y-TOC	17.5	2
6	Ileal NET		Y-TOC	11.0	2
7	Ileal NET	TACE	Y-TOC	13.2	1
8	Pancreas NET	Diabetes	Y-TOC	23.8	2
9	Paraganglioma		Lu-TATE	27	3
10	Ileal NET	TACE + CH	Y-TOC	17.9	2
11	Stomach NET		Y-TOC	7.7	1
12	Duodenum NET		Lu-TATE	21	3
13	Ileal NET		Y-TOC	12.8	2
14	Medullary thyroid carcinoma		Y-TOC	8.9	2
15	Ileal NET		Y-TOC	12.7	1
16	Pancreas NET	CH	Y-TOC	10.1	1
17	Medullary thyroid carcinoma		Y-TOC	3.8	1
18	Meningioma		Lu-TATE	22.3	3
19	Ileal NET	TACE	Y-TOC	13.3	2
20	Appendix NET		Lu-TATE	23.2	3
21	Ileal NET	Renal and adrenal mets	Y-TOC	12.5	2
22	Unknown NET		Y-TOC	5.4	1
23	Breast carcinoma	TACE, CH	Y-TOC	9.2	2
24	Pancreas NET	HT	Y-TOC	9.6	2
25	Pancreas NET	CH, abdomen RT	Y-TOC	12.2	1
26	Medullary thyroid carcinoma		Y-TOC	6.4	1
27	Ileal NET	HT, TACE, peri-renal mets	Y-TOC	7.4	1
28	Ileal NET		Y-TOC	14.4	2

NET=neuroendocrine tumour;TACE=trans arterial chemo-embolisation; HT=hypertension; CH= chemotherapy; RT=radiotherapy; Protocol number: see Methods.

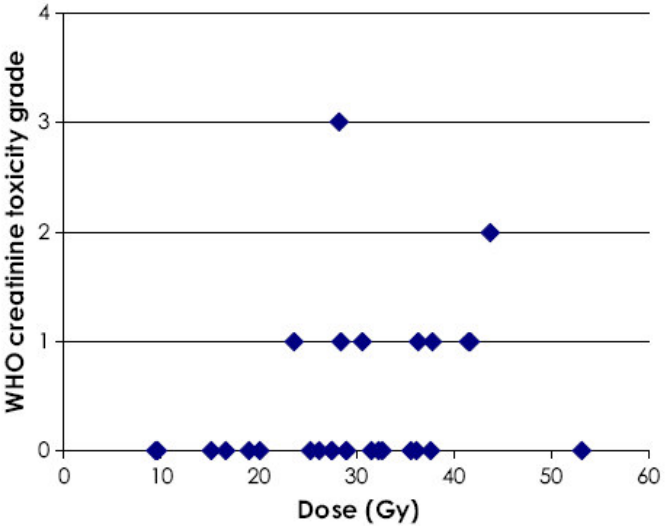
Table 2. Kidney parameters, absorbed doses and BED evaluated in patients who underwent a specific dosimetric study (median value, range of variation).

	^{90}Y-DOTATOC	^{177}Lu-DOTATATE
Kidney masses (g)	210–335 g (10 female patients)	200–275 g (3 female patients)
	285–380 g (13 male patients)	320–395 g (2 male patients)
$T_{1/2\ eff}$ (h)	30 (26–44)	57 (42–65)
No of cycles	6 (2–11)	6 (4–6)
Cumulative activity (GBq)	12.2 (3.8–23.8)	26.6 (21.3–43.5)
Kidney-absorbed dose per unit activity (Gy/GBq)	2.5 (1.3–4.9)	0.9 (0.5–1.7)
Cumulative absorbed dose to the kidneys (Gy)	31 (10–53)	21 (15–23)
Cumulative BED to the kidneys (Gy)	39 (11–67)	19 (16–38)

Table 3. Characteristics of of the 28 patients, as regards administered activity, kidney dose, kidney BED and toxicity.

Patient #	Tumour	Risk factors	Therapy	Cumulative activity (GBq)	Cumulative dose (Gy)	Cumulative BED (Gy)	Numbers of cycles	Toxicity	Toxicity grade	Recover
1	Pancreas NET	Yes	Y-TOC	11.5	29.1	33.7	6	No		
2	Medullary thyroid carcinoma		Y-TOC	19.2	53.2	66.5	9	No		
3	Bronchial NET	Yes	Y-TOC	12.2	23.7	29.5	4	Yes	1	No
4	Bronchial NET		Lu-TATE	29.2	15.2	16.1	6	No		
5	Pancreas NET		Y-TOC	17.5	28.9	33.2	8	No		
6	Ileal NET		Y-TOC	11.0	28.4	39.2	3	Yes	1	Yes
7	Ileal NET	Yes	Y-TOC	13.2	37.8	45.8	6	Yes	1	No
8	Pancreas NET	Yes	Y-TOC	23.8	41.5	47.0	11	Yes	1	No
9	Paraganglioma		Lu-TATE	27	16.6	17.7	6	No		
10	Ileal NET	Yes	Y-TOC	17.9	32.2	36.6	8	No		
11	Stomach NET		Y-TOC	7.7	35.5	49.4	3	No		
12	Duodenum NET		Lu-TATE	21	19.1	21.3	4	No		
13	Ileal NET		Y-TOC	12.8	31.6	38.7	5	No		
14	Medullary thyroid carcinoma		Y-TOC	8.9	26.2	37.5	2	No		
15	Ileal NET		Y-TOC	12.7	27.6	31.1	8	No		
16	Pancreas NET	Yes	Y-TOC	10.1	41.7	47.4	11	Yes	1	No
17	Medullary thyroid carcinoma		Y-TOC	3.8	9.5	11.0	2	No		
18	Meningioma		Lu-TATE	22.3	37.8	43.5	6	No		
19	Ileal NET	Yes	Y-TOC	13.3	36.4	42.9	7	Yes	1	No
20	Appendix NET		Lu-TATE	23.2	20.2	22.0	6	No		
21	Ileal NET	Yes	Y-TOC	12.5	27.5	32.7	6	No		
22	Unknown NET		Y-TOC	5.4	9.7	10.5	4	No		
23	Breast carcinoma	Yes	Y-TOC	9.2	30.6	41.1	3	Yes	1	No
24	Pancreas NET	Yes	Y-TOC	9.6	32.8	38.9	5	No		
25	Pancreas NET	Yes	Y-TOC	12.2	43.8	55.2	6	Yes	2	No
26	Medullary thyroid carcinoma		Y-TOC	6.4	25.2	30.5	4	No		
27	Ileal NET	Yes	Y-TOC	7.4	28.2	33.0	6	Yes	3	No
28	Ileal NET		Y-TOC	14.4	36.2	44.4	7	No		
Min				3.8	9.5	10.5	2.0			
Max				29.2	53.2	66.5	11.0			
Median				12.6	29.0	37.1	6.0			

Fig. 1. Creatinine toxicity in the 23 patients treated with ^{90}Y-DOTATOC



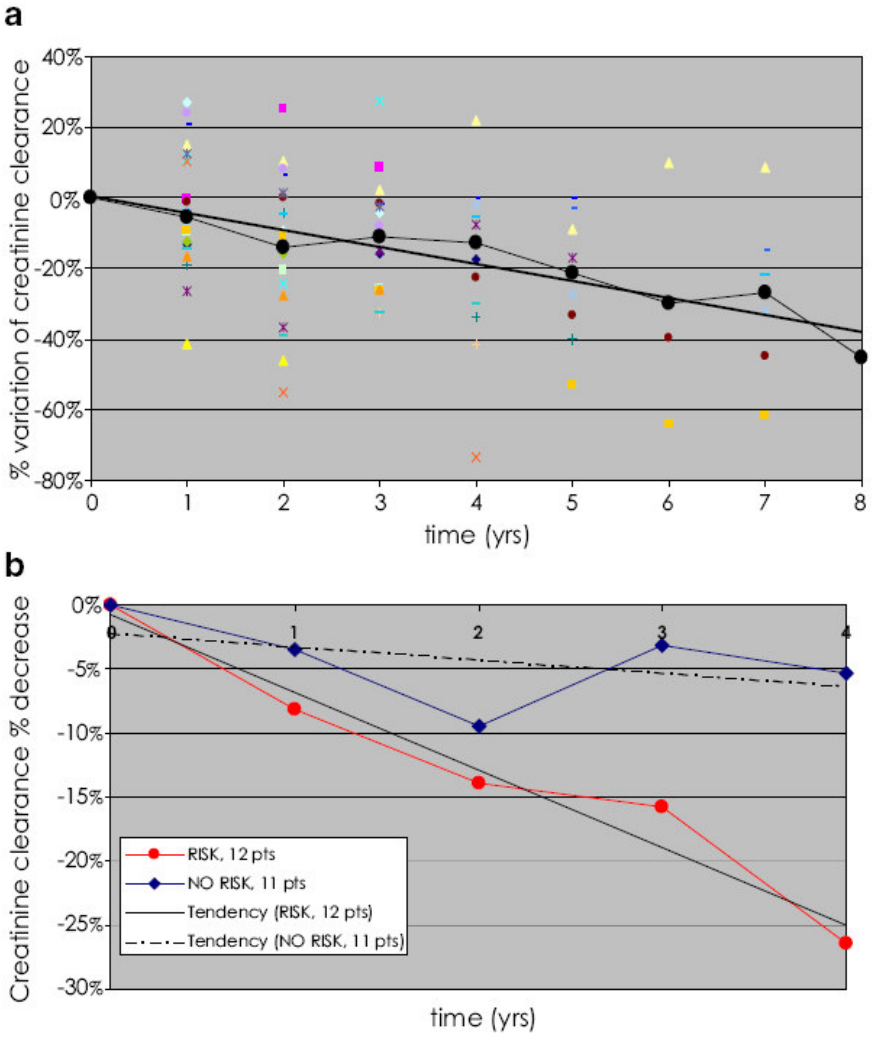


Fig. 2A. Creatinine clearance course (pts, median, tendency) in the 23 patients treated with ^{90}Y-DOTATOC over 8 years of follow up (R^2=0.8909).

Fig. 2B. Fig. 2B. Different median creatinine clearance course in risk (red line, tendency continuous line) and no risk (blue line, tendency dotted line) patients treated with ^{90}Y-DOTATOC, over 4 years of follow up (R2=0.9598)

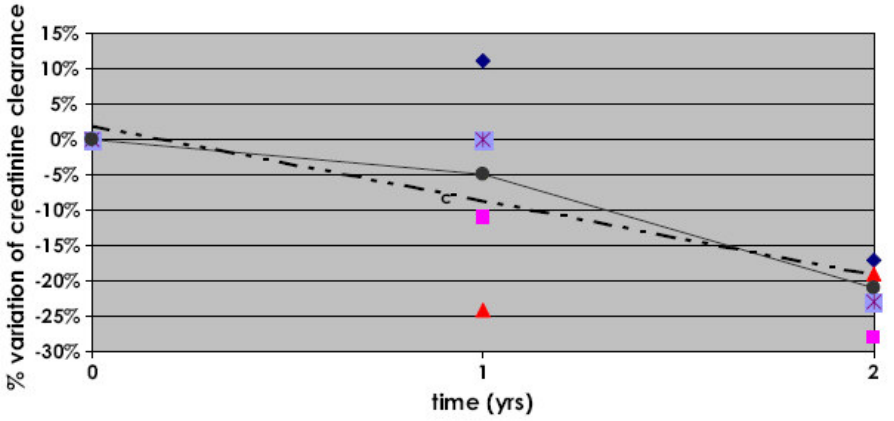


Fig. 3. Creatinine clearance course (pts, median, tendency) in the five patients treated with ^{177}Lu-DOTATATE over 2 years of follow up (R^2= 0.916)

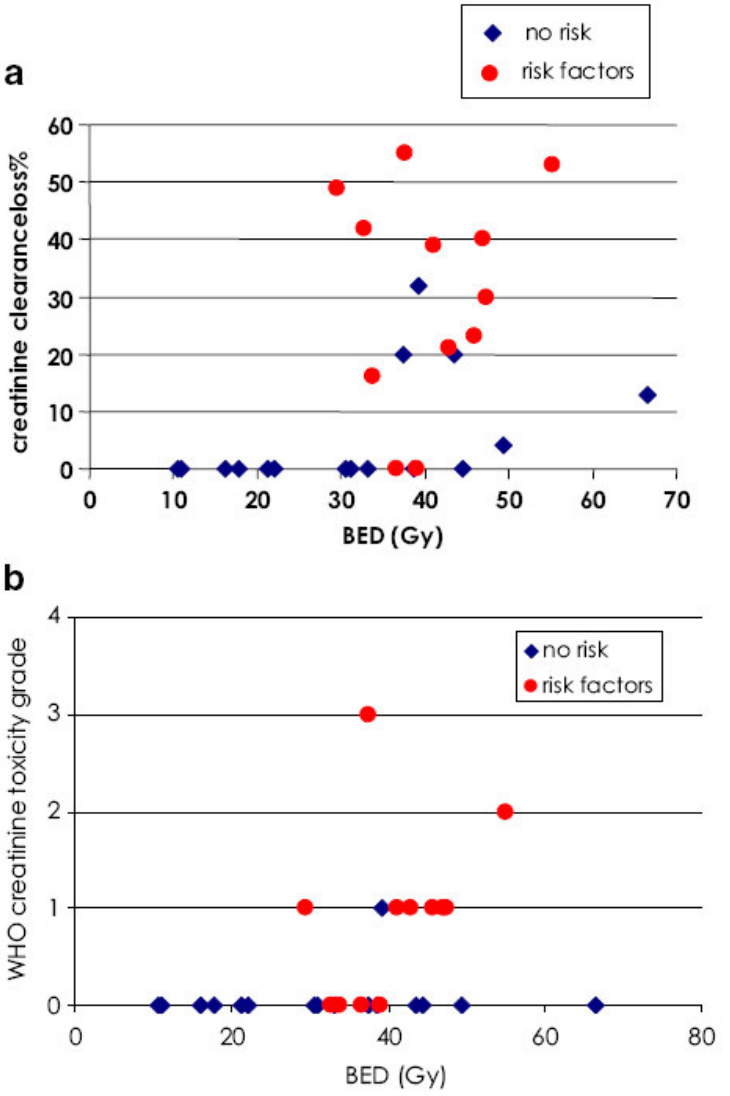


Fig. 4A. Creatinine clearance loss % according to the renal BED in the risk (red dots) and no risk (blue dots) patients treated with ^{90}Y-DOTATOC

Fig. 4B. Creatinine toxicity according to the renal BED in the risk (red dots) and no risk (blue dots) patients treated with ^{90}Y-DOTATOC

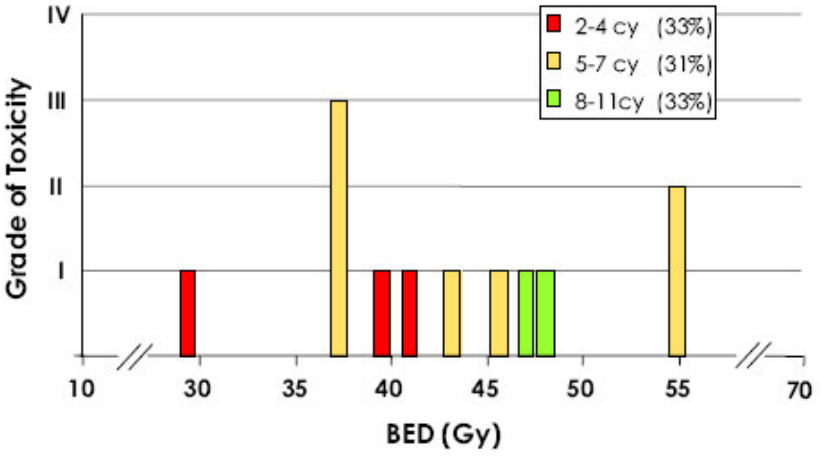


Fig. 5. Creatinine toxicity according to the renal BED in the patients treated with ^{90}Y-DOTATOC: results in various categories of activity fractionation.